Review of the Prior Prosecution

In order to properly address the rejections below, Applicants believe that a brief review of the prior prosecution in this patent application is appropriate.

Previously, the claims now presented were rejected as allegedly obvious over Sasaki, et al., *J. Biochem.*, 86:1537-1548 (1979) ("Sasaki '79") or Sasaki, et al., *J. Biochem.*, 91:1551-1561 (1982) ("Sasaki '82") in view of Kasche, et al., *J. Chromatogr.*, 510:149-154 (1990) ("Kasche"), Teichberg, *J. Chromatogr.*, 510:49-57 (1990) ("Teichberg") and Jost, et al., *Biochem. Biophys. Acta*, 362:75-82 (1974) ("Jost"). See Examiner's Answer, Paper No. 15; Advisory Action, Paper No. 12; and Final Office Action, Paper No. 8. This rejection was primarily premised upon the two Sasaki references which disclose an Amberlite CG-50 resin which is a resin having carboxyl groups attached thereto. Applicants appealed this rejection to the Board of Patent Appeals and Interferences (hereinafter "Board"). See Reply Brief of July 12, 1999; Appeal Brief of May 10, 1999. On appeal, the Board found the rejection to be inadequate, and accordingly reversed the decision of the Examiner. See Decision on Appeal, Paper No. 19, page 4.

In reversing the Examiner, the Board acknowledged that each of the Sasaki references "lacks performing the process with a resin that undergoes the transition between uncharged and charged between pH values of 5 to 9." Decision on Appeal, Paper No. 19, pages 4 and 5. Accordingly, the Board found that "neither Sasaki reference describes a resin which meets the requirements of the claims on appeal." Decision on Appeal, Paper No. 19, page 5.

Applicants note that the claims currently pending are the same as those that went on appeal to the Board and found not to be anticipated or rendered obvious by the Sasaki references.

Rejection under 35 U.S.C. § 102(b)

Claims 1, 2, 4, 5, 10-16, 18, 20, 22, and 23 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Boardman et al., *Nature*, 171:208-210 (1953) ("Boardman"). According to the Examiner, the Boardman reference discloses the separation of proteins, in particular cytochrome c, using Amberlite IRC-50, an ion exchange media comprised of cross-linked poly(methacrylic acid). The Examiner has alleged that at a low pH cytochrome c binds to the cation exchange media which has uncharged carboxylic groups. The Examiner has further alleged that at a pH of 6 to 7, the protein elutes from the column. Office Action, Paper No. 20, page 2. Applicants respectively traverse this rejection for the following reasons.

To anticipate a claim, a single prior art reference must teach, either expressly or inherently, each and every element of the claimed invention. See M.P.E.P. § 2131; Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987); Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986). For the reasons noted below, Boardman fails to teach each and every limitation of the claimed invention.

Specifically, central to the claimed compositions is the use of an electrostatically uncharged resin at the pH where the target protein or peptide is bound to the resin which pH is in the range of from 5 to 9. In addition, the resin is selected such that it contains an electrostatic charge at the pH where the protein or peptide is desorbed from the resin wherein the desorption occurs by a change in the pH from the binding pH.

In contrast, the Boardman reference fails to teach binding of the protein at a pH of 5 to 9 and further fails to teach that the resin is uncharged at such pHs. The Office Action admits to this at page 2 wherein it states that "at a low pH the cation exchange media is uncharged and binds the proteins." No basis is seen in the Office Action or in Boardman

to conclude that Boardman teaches binding a protein to an uncharged resin in the range of pH 5 to 9.

In point of fact, Applicants submit that these teachings of Boardman are further removed from the claimed invention than those of Sasaki which the Board maintained did not obviate or anticipate the now presented claims. Specifically, Sasaki disclosed that the Amberlite CG-50 resin was **uncharged** only at **pHs of about 4.5 or less**. Contrarily, Boardman states that his resins are uncharged only at "very low pHs." Boardman, page 209, 1st column, 4th full paragraph. Based on this recitation, one skilled in the art cannot reasonably conclude that a very low pH reads of pHs from **5 to 9**. Accordingly, the Boardman reference is even further removed from the claimed invention than the Sasaki references which the Board held did not anticipate or obviate the claimed invention. See Decision on Appeal, Paper No. 19, pages 4 and 5.

In further support of the fact that Boardman fails to meet the claimed limitations, Applicants submit the Declaration under 37 C.F.R. § 1.132 by Nathaniel T. Becker, one of the inventors of the subject matter disclosed and claimed in the present application (hereinafter the "Becker Declaration"). The Becker Declaration discusses the Amberlite IR-50 resin utilized in Boardman. This declaration also explains the product literature for the Amberlite IRC-50 resin that was provided by the manufacturer, Rohm and Haas, Co. (2000) (hereinafter "Rohm and Haas") See, Becker Declaration, Exhibit B.

As set forth in the declaration, the Amberlite IRC-50 is a weakly acidic cation exchange resin based on macroreticular methacrylic acid-divinylbenzene chemistry. It has a pK value of 6.1, meaning that it is still 50% charged at pH 6.1 The charged moiety on the resin is a carboxylic acid group within the methacrylic acid functionality. Given that the resin is weakly acidic, it retains a partial charge at pH 5, and becomes fully protonated (neutralized) only at a pH of between 2.5 and 4.0, depending on the buffer salts present. This is clearly demonstrated in the Rohm and Haas product literature. As evident in

Figure 3 of Rohm and Haas, the point of zero net charge is equivalent to the pH at which zero millequivalents of base (KOH) have been applied to the resin, which is represented by where the titration curves intersect the y-axis (pH) at zero on the x-axis (mEq KOH). This will vary slightly depending on the buffer salts, but, at most, is pH 4.0 for pure water. Accordingly, the Becker Declaration confirms that the Amberlite IRC-50 resin in Boardman remains charged at the pH where it binds the protein.

Therefore, Boardman fails to anticipate the claimed invention, because the reference does not meet each and every limitation of the claims. In view of the above, Applicants respectively request the withdrawal of the rejection.

Rejection under 35 U.S.C.§ 103(a)

Claims 1-5 and 7-23 stand rejected under 35 U.S.C. § 103(a) as allegedly obviousness over Boardman et al., *Nature*, 171:208-210 (1953) ("Boardman"), Sasaki et al., *J. Biochem.*, 86:1537-1548 (1979) ("Sasaki 1979") and Sasaki et al., *J. Biochem.*, 91:1551-1561 (1982) ("Sasaki 1982") in view of Kunin, Ion Exchange Resins, 34-39 (John Wiley & Sons, Inc., Interscience 1958) ("Kunin"), Topp et al., *J. Chem. Soc.*, Pt. 2:3299-3303 (1949) ("Topp"), Kitchener, Ion Exchangers In Organic and Biochemistry, 63-64 (Calmon and Kressman eds., Interscience Publishers, Inc. 1957) ("Kitchener") and Guthrie, Ion Exchangers In Organic and Biochemistry, 558-559 (Calmon and Kressman eds., Interscience Publishers, Inc. 1957) ("Guthrie"). Applicants respectively traverse this rejection for at least the following reasons.

To establish a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion or motivation in the reference to combine either the references themselves or to modify or combine the reference teachings. See M.P.E.P. § 2143; In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). This element requires that the Examiner must show "some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art that would lead that

individual to combine the relevant teachings of the references." In re Fine, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). In other words, the Examiner must provide a logical reason as disclosed in the prior art at the time of the invention for combining the references along the lines of the invention; otherwise the use of such teachings as evidence of non-obviousness will entail impermissible hindsight. Ex parte Stauber and Eberle, 208 U.S.P.Q. 945, 946 (Bd. App. 1980). Second, the prior art must provide a reasonable expectation of success. See M.P.E.P. § 2143.02; Vaeck, 947 F.2d at 488, 20 U.S.P.Q.2d at 1438; In re Merck & Co., Inc., 800 F.2d 1091, 231 U.S.P.Q. 375 (Fed. Cir. 1986). Third, the prior art references must teach or suggest each and every element of the claimed invention. See M.P.E.P. § 2143.03; In re Royka, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974); In re Wilson, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). Applicants believe that a *prima facie* case of obviousness has not been made.

To start, Applicants note that the same claims that went to the Board on appeal now stand rejected as allegedly obvious over a combination of references that includes the same two Sasaki articles (utilized once again as primary references) that the Board previously maintained did not obviate or anticipate the claimed invention. Applicants submit that the Sasaki references are no more applicable to the rejection now than they were when the Board found that they did not anticipate or obviate the claimed invention.

As discussed above, the Board found that each Sasaki reference "lacks performing the process with a resin that undergoes the transition between uncharged and charged between pH values of 5 to 9." Decision on Appeal, Paper No. 19, pages 4 and 5. According to the Board, "neither Sasaki reference describes a resin which meets the requirements of the claims on appeal." Decision on Appeal, Paper No. , page 5. Thus, the Board held that the Sasaki articles were not pertinent to the claimed invention, because neither one discloses or suggests methods which recover protein or peptides by binding the protein or peptides to a electrostatically uncharged resin at physiological pHs of from 5 to

9 after which the protein or peptides are then recovered from the resin merely by changing the pH to effect desorption. This failure of Sasaki to suggest such resins is recognized in the current Office Action at pages 4 and 5 ("Sasaki et al. (1979) [Sasaki (1982)] lack forming the complex with a resin that is uncharged between pH values of 5-9."). For this reason alone, the Sasaki articles are not applicable to this rejection.

Furthermore, in addition to Sasaki's failing to disclose or suggest the limitations of the claims, Applicants believe that these references in fact "teach away" from the claimed invention. Specifically, the cited Sasaki articles lead to the conclusion that the employed ionizable Amberlite CG-50 resins are **charged** at any pH within the claimed pH range from 5 to 9, because the Sasaki articles indicate that a pH of 4.5 or less is required to completely protonate the carboxyl groups of the resins. Accordingly, at a pH of 5 or more, Sasaki's Amberlite CG-50 resins would carry an anionic charge. Sasaki himself recognized this limitation at page 1561 of his 1982 article where he states that:

> "However, hydrophobic-ionic chromatography with Amberlite CG-50 has the disadvantage that a pH as acidic as 4.5 is required in the process of adsorption."

As such, it would appear that the both Sasaki references are limited to Amberlite resins which would bind the protein or peptides at pHs of 4.5 or less. This clearly leads one of ordinary skill in the art away from the claimed invention which calls for the use of **uncharged resins** that bind proteins in a medium with a **pH of 5 to 9**.

It is well established that a prior art teaching must be considered as a whole including portions that "teach away" from the claimed invention. See M.P.E.P. § 2141.02; W.L. Gore & Associates, Inc., v. Garlock, Inc., 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). Moreover, it is well established that references cannot be combined where the references teach away from their combination. M.P.E.P. § 2145; In re Grasselli, 713 F.2d 731, 743, 218 U.S.P.Q. 769, 779 (Fed. Cir. 1983). The totality of the prior art must be considered, and proceeding

contrary to accepted wisdom in the art is evidence of non-obviousness. M.P.E.P. § 2145; In re Hedges, 783 F.2d 1038, 228 U.S.P.Q. 685 (Fed. Cir. 1986).

Given Sasaki's teaching away, the Sasaki references cannot now be properly combined with the remaining references to arrive at the claimed invention. In addition, such a teaching away also means that the references clearly fail to provide a reasonable expectation to one of ordinary skill in the art of successfully arriving at the claimed invention upon a reading of the prior art.

At best, Sasaki (1982) merely discloses the possibility of absorbents carrying alkaline groups instead of carboxyl groups although, as described by Sasaki (1982), the "relationship to pH would be opposite." Such an opposite relationship suggests to one of ordinary skill in the art an alkaline pH as far removed from neutrality (pH 7) as the Amberlite resins described by Sasaki (1982). Since Sasaki's Amberlite resins are reported to dissociate at pH 4.5, opposite alkaline charges would dissociate at pH 9.5 which is also outside the range claimed by Applicants.[1]

Accordingly, the Sasaki (1982) article would not provide the requisite motivation to the skilled artisan to employ ionizable functionalities which would dissociate at pHs of from 5 to 9. Sasaki (1982) merely suggests at best alkaline groups which be opposite carboxyl groups. However, there is no basis to assert why groups which dissociate at pH 5 to 9 as per this invention would be "opposite" such carboxyl groups. Thus, Sasaki (1979) and Sasaki (1982) fail to provide the requisite motivation to one of ordinary skill in the art to arrive at the claimed composition, and they actually teach away from the claimed composition. In view of these arguments, the two Sasaki references, alone, or in combination with each other, in combination with Boardman or in combination with any of

[1] The acidic pH of 4.5 is 2.5 units removed from a neutral pH of 7 and, accordingly, a basic pH equally removed from neutrality would require a pH of 9.5.

the cited secondary references (discussed more fully below) do not render obvious the claimed invention.

Applicants again remind the Office that each of these points regarding both Sasaki references were already successfully argued to the Board in the appeal for this case. Thus, in accordance with the Board's prior decision and the arguments set forth above, the two Sasaki articles are not applicable to this rejection. Applicants submit that this turf once plowed is not available for plowing again.

As to Boardman (the other primary reference), Applicants submit that the reference does not obviate or anticipate the now presented claims. In particular, the reference fails to teach binding of the protein at a pH of 5 to 9 and further fails to teach that the resin is uncharged at such pHs. The Office Action admits to this at page 2 wherein it states that "at a low pH the cation exchange media is uncharged and binds the proteins." Along these lines, the Office Action provides no basis to conclude that Boardman teaches binding a protein to an uncharged resin in the range of from pH 5 to 9.

In fact, Applicants submit that Boardman is even further removed from the claimed invention than Sasaki which the Board maintained did not obviate or anticipate the now presented claims. As previously discussed, Sasaki disclosed that the Amberlite CG-50 resin was uncharged only at pHs of about 4.5 or less. This is also confirmed by the Becker Declaration as discussed above. Contrarily, Boardman states that his resins are uncharged only at "very low pHs." Boardman, page 209, 1st column, 4th full paragraph. Based on this recitation, one skilled in the art cannot reasonably conclude that a very low pH reads of pHs from 5 to 9. Accordingly, the teaching of Boardman is contrary to that of the claimed invention.

Furthermore, Boardman also indicates that adsorption of cytochrome c occurs at a low pH. This is a clear teaching away from the claimed resin-protein/peptide complex that

requires binding of the protein or peptide to the electrostatically uncharged resin at a pH of 5 to 9. Given this teaching away, the Boardman reference cannot be properly combined with the secondary references to arrive at the claimed composition. In addition, such a teaching away also means that the reference completely fails to provide a reasonable expectation to one of ordinary skill in the art of successfully arriving at the claimed composition.

Therefore, the Boardman reference, alone, or in combination with the Sasaki references or in combination with any of the cited secondary references (discussed more fully below) does not render obvious the claimed invention.

The secondary references of Kunin (1958), Topp (1949), Kitchener (1957) and Guthrie (1957) fail to remedy the above-noted deficiencies of the primary references.

The Kunin article merely relates to a discussion of titration curves of several ion exchange media, including the titration curve of the carboxylic acid cation exchange resin, Amberlite IR-105. (Kunin, page 37, Figure 13). While it is true that this resin is same resin used in Boardman, this teaching does not remedy the deficiencies of the Boardman reference. Namely, it fails to teach or suggest a resin-protein/peptide complex wherein the resin is electrostatically uncharged at a pH where the target protein or peptide is bound to the resin and wherein the protein or peptide binds the resin at a pH of 5 to 9.

Likewise, the remaining secondary references (i.e., Topp, Kitchener, and Guthrie) share the same fate as the Kunin article. For instance, the Topp article relates to the titration of several ion exchange resins containing known ionizable groups. Figure 2 at page 3301 shows titration with cross-linked poly(methacrylic acid). The reference concludes that such cation exchanger containing carboxyl groups behave as weak acids, i.e., the uptake of sodium ion is dependent on pH. However, the Topp article fails to teach or suggest a resin-protein/peptide complex wherein the resin is electrostatically

uncharged at a pH where the target protein or peptide is bound to the resin and wherein the protein or peptide binds the resin at a pH of 5 to 9.

The Kitchener reference at page 63 discloses that carboxylic acid functional groups titrate with KOH between pH 7 and 11 with a midpoint of about 9. However, the reference fails to teach or suggest a resin-protein/peptide complex wherein the resin is electrostatically uncharged at a pH where the target protein or peptide is bound to the resin and wherein the protein or peptide binds the resin at a pH of 5 to 9.

The Guthrie reference merely lists the pH at half capacity for a number of ion exchange cotton fabrics. According to Table I in Guthrie, the various modifying groups have pH at half capacity ranging from 1.5 to 12. However, the reference fails to teach or suggest a resin-protein/peptide complex wherein the resin is electrostatically uncharged at a pH where the target protein or peptide is bound to the resin and wherein the protein or peptide binds the resin at a pH of 5 to 9.

It appears that the Examiner has relied on these secondary references as allegedly disclosing media which can be used in the claimed pH range of 5 to 9. For instance, the Office Action states "[m]edia containing ionizable groups in concert with non-ionizable groups are well-known" and that it would constitute nothing more than routine optimization to select suitable ion exchange media compatible with the target protein and having ionizable functional groups in the desired pH range of 5 to 9. Office Action, Paper No. 20, page 6. This is an attempt to use an "obvious to try" rationale to arrive at the claimed method steps. The rejection utilizes multiple references providing numerous possible choices. However, none of the references give direction as to which parameters are crucial nor do they indicate which one of the many possibilities is likely to succeed. Moreover, it is well established that in moving from the prior art to the claimed invention, one cannot base a determination of obviousness on what one of ordinary skill in the art might try or find obvious to try. In re O'Farrel, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673, 1681 (Fed.

Cir. 1988). Indeed, the proper test requires determining what the prior art would have led the skilled artisan to do. However, as previously discussed, each of the cited secondary references fails to teach or suggest a resin-protein/peptide complex wherein the resin is electrostatically uncharged at a pH where the target protein or peptide is bound to the resin and wherein the protein or peptide binds the resin at a pH of 5 to 9. Hence, the secondary references fail to cure the deficiencies of Boardman, Sasaki (1979), and Sasaki (1982).

Therefore, nothing in the cited prior art references teaches or suggests the elements of the claimed composition. Nor do these references, either alone or in combination, provide a reasonable expectation of success to a skilled artisan that the modifications necessary to the prior art references to arrive at the claimed invention would be successful in effecting protein recovery. Absent such suggestion and reasonable expectation of success, this rejection is believed to be error. Vaeck, 947 F.2d at 488, 20 U.S.P.Q.2d at 1438. Furthermore, the mere fact that the Examiner had to combine seven references in an attempt to arrive at the claimed invention is indicative of the non-obviousness of the claimed invention. Thus, for the reasons noted above, Applicants respectively request the withdrawal of this rejection.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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Date: January 28, 2001